COMMENTS AND RESPONSES

Response to Bodmer et al. Metformin and the Risk of Cancer: Time-Related Biases in Observational Studies. Diabetes Care 2012;35: 2665–2673

In the comment by Bodmer et al. (1), the authors question our assertion that several of their studies suffered from time-window bias (2). Perhaps there are subtleties about this bias that need to be further clarified.

In the authors' breast cancer study (3), cases and controls were matched on age, sex (although all females), general practice, and index date (i.e., the calendar date of the breast cancer diagnosis). However, there was no matching on time since diabetes diagnosis or since the first prescription for an oral hypoglycemic agent. Not matching on this entry point can result in artificially different exposure patterns between cases and controls (a patient with 5 years' diabetes duration has a greater chance of receiving a given drug than a patient with only 1-year duration), thus introducing time-window bias (4). Unlike immortal time bias, it is not possible, a priori, to predict the direction of this bias on the point estimates since it directly depends on the differential durations for exposure assessment in the cases and controls. In their letter, the authors state that the length of time in the database was similar between the breast cancer cases and controls (not mentioned in the article). This simply means that *on average*, cases and controls had similar durations, which can explain the overall null association observed with the use of metformin (odds ratio [OR] = 1.03). However, it is possible that in certain subgroups such as patients who received ≥40 prescriptions of metformin, the duration of treated diabetes happened to be shorter in cases than in controls, resulting in OR = 0.44. Note the ORs were all above 1.00 for the other prescription categories, including those who received between 10–39 metformin prescriptions (OR = 1.09). To clarify this, it would be necessary to calculate the average duration of *treated diabetes* for the 17 cases and 120 controls, along with the referent nonusers, that generated this strong risk reduction. Moreover, the approach used by the authors to adjust for duration of diabetes was too crude and not the most appropriate one to address time-window bias. Finally, the authors raise the issue that any differential exposure opportunity would have affected the other antidiabetic agents as well. Here again, one would need to compare the durations of *treated diabetes* for the other antidiabetic agent subgroups and the respective nonusers.

In other metformin studies conducted by the authors, cases and controls were matched on length of time in the database (5). While this may be an improvement over the breast cancer study (3), this method is still prone to time-window bias. Length of time in the database simply means that cases and matched controls have been registered in the database for the same amount of time. It does not guarantee the same duration of treated diabetes in cases and controls that would avoid time-window bias.

In all, we thank the authors for this opportunity to clarify the bias and hope our article provides some methodological guidelines useful to avoid some of the vexing time-related biases in observational studies of important drug effects.

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References

1. Bodmer M, Jick SS, Meier CR. Comment on: Suissa and Azoulay. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care 2012; 35:2665–2673 (Letter). Diabetes Care 2013;36:e85. DOI: 10.2337/dc12-2693
2. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care 2012;35: 2665–2673
3. Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Long-term metformin use is associated with decreased risk of breast cancer. Diabetes Care 2010;33:1304–1308
4. Suissa S, Dell'aniello S, Vahey S, Renoux C. Time-window bias in case-control studies: statins and lung cancer. Epidemiology 2011;22:228–231
5. Bodmer M, Becker C, Meier C, Jick SS, Meier CR. Use of metformin is not associated with a decreased risk of colorectal cancer: a case-control analysis. Cancer Epidemiol Biomarkers Prev 2012;21:280–286